Novartis Pharmaceuticals Corporation

59 Route 10

East Hanover, NJ 07936

Appendix 9:
Dear Doctor Letter

Zometa® (zoledronic acid) Injection

and

Aredia® (pamidronate disodium) Injection

Submitted: February 1, 2005

Oncologic Drugs Advisory Committee Meeting

March 4, 2005

Novartis Oncology
One Health Plaza
East Hanover, NJ 07936

NOVARTIS ONCOLOGY

September 24, 2004

Dear Doctor:

Novartis is fully committed to assuring timely dissemination of safety information about their products to the healthcare community. We are writing to inform you of changes made to the **Precautions** and **Post-Marketing Experience** sections of the Aredia® (pamidronate disodium) Injection and Zometa® (zoledronic acid) Injection prescribing information.

These changes relate to spontaneous reports of osteonecrosis of the jaw (ONJ), mainly in cancer patients, who have received bisphosphonates as a component of their therapy.

In the U.S. Package Insert for both Aredia and Zometa, the following information on osteonecrosis of the jaw has been added under the **Precautions** Section.

Precautions

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

In the U.S. Package Insert for both Aredia and Zometa, the following information on osteonecrosis had previously been added to the **Adverse Reactions** section under **Post-Marketing Experience**.

> **Post-Marketing Experience**
>
> Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS)

Healthcare professionals should report all serious adverse events suspected to be associated with the use of Aredia or Zometa to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover NJ 07936 or by phone (888-NOW NOVARTIS or 888 669 6682) or the internet at http://www.novartis.com

Alternatively this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

Please see enclosed revised package inserts for complete prescribing information for both Aredia and Zometa.

Please contact Novartis Oncology Medical Services at 1-888-669-6682 if you have further questions.

Sincerely,

John A. Hohneker, MD
VP, Novartis Oncology Medical Affairs & Services
One Health Plaza
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